25. (amended) The method of claim 22, wherein [said] the patient is a cancer patient preparing to undergo chemotherapy or radiation therapy.

26. (amended) The method of claim 22, wherein [said] the patient is a cancer patient currently undergoing chemotherapy or radiation therapy.

27. (amended) The method of claim 1, wherein [said] the mucositis is oral mucositis.

Remarks

Information Disclosure Statement

It is noted that some of the references listed in the PTO 1449 forms have been considered. Consideration of the remainder would be greatly appreciated.

Amendments to the Claims

The claims have been narrowed to a method of administering the combination of an NSAID, an inflammatory cytokine inhibitor, or a mast cell inhibitor and an effective amount of an MMP inhibitor to treat mucositis induced by chemotherapy or radiation.

Rejections under 35 U.S.C. 102

Claims 15 and 19 were rejected under 35 U.S.C. 102(b) as disclosed by Schenk, et al., Clin. Oral Implants Res. 8(5):427-433 (1997) or Rothwell, et al., Spec. Care Dentist. 10(1):21-25 (1990). These rejections are respectfully traversed if applied to the amended claims.

It is understood that all claims are pending but only those drawn to the elected species of IL-6 or pentoxifylline were examined, claims 1, 4-7, 12-15, and 19-27, pending allowance of claims to the elected species.

Schenk, et al.

Schenk, et al. relates to treatment of periodontal disease, not mucositis induced by radiation or chemotherapy. Accordingly, Schenk, et al. does not anticipate the claims as amended.

Rothwell, et al.

Rothwell administers a combination of hydrocortisone, nystatin, tetracycline, and diphenhydramine to treat mucositis. The claims now require the combination of an NSAID, an inflammatory cytokine inhibitor, or a mast cell inhibitor and an MMP inhibitor. Rothwell does not disclose an NSAID, an inflammatory cytokine inhibitor or a mast cell inhibitor. Accordingly, Rothwell does not disclose the claimed method as defined by the amended claims.

Rejections under 35 U.S.C. 103

Claims 1, 4-6, 12-14, and 22-27 were rejected under 35 U.S.C. 103 as obvious over Schenk, et al., or Rothwell, et al., in view of Tilg, et al., Transplantation 56(1), 196-201 (1993). Claim 20 was rejected under 35 U.S.C. 103 as obvious over Schenk, et al., or Rothwell, et al., in combination with U.S. Patent No. 6,239,119 to Stogniew, et al. These rejections are respectfully traversed.

Schenk and Rothwell are discussed above. Neither Tilg, et al., nor Stogniew make up for the deficiencies of Schenk or Rothwell. Tilg, et al., discloses treating patients with pentoxifylline to reduce TNF-alpha production and thereby the side effects associated with bone marrow transplantation. Stogniew discloses administering a radioprotectant, which may also include any of a number of excipients and other actives. None of Schenk, Rothwell, Tilg, et al. or Stogniew disclose an effective amount of MMP inhibitor to treat mucositis, nor is there any teaching that one should select an NSAID, an inflammatory cytokine inhibitor, or a mast cell

inhibitor to combine with an MMP inhibitor to treat mucositis, nor that one would have an expectation of success using the claimed combination since there is no teaching that would lead one to use a tetracycline, much less one in an amount effective in and of itself to prevent or reduce mucositis due to radiation and/or chemotherapy. Accordingly, even in combination, Schenk, Rothwell, Tilg, et al. and Stogniew do not disclose nor make obvious the claimed method.

Allowance of claims 1-7, 10-14, and 23-27, as amended, is earnestly solicited.

Respectfully submitted,

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CERTIFICATE OF FACSIMILE (37 CFR 1.8a)

I hereby certify that this Amendment, along with any paper referred to as being attached or enclosed, is being facsimile transmitted to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Date: November 13, 2002

Jean Hicks

APPENDIX: Marked up copy of claims as amended

1. (amended) A method of treating, inhibiting, or preventing mucositis in a human patient, [said method] comprising administering to [said] a patient in need of or undergoing radiation treatment or chemotherapy, [first and second different therapeutic agents, wherein said first therapeutic agent is] an NSAID, an inflammatory cytokine inhibitor, or a mast cell inhibitor[; and said second therapeutic agent is an inflammatory cytokine inhibitor, a mast cell inhibitor,] in combination with an effective amount of an MMP inhibitor[, an NSAID, or an NO inhibitor] to alleviate the symptoms of the mucositis.

2. (amended) The method of claim 1, [wherein at least one of said first and second agents is an] comprising administering as the NSAID [which is] a COX-1 or COX-2 inhibitor.

3. (amended) The method of claim 2, wherein [said] the COX-1 inhibitor is indomethacin or flurbiprofin.

4. (amended) The method of claim 1, [wherein the first agent is an] comprising administering an inflammatory cytokine inhibitor selected from the group consisting of an IL-6 inhibitor, a TNF-alpha inhibitor, an IL-1 inhibitor, and an interferon-gamma inhibitor.

5. (amended) The method of claim 4 wherein the [first agent] inflammatory cytokine inhibitor is a TNF-alpha inhibitor [and the second agent is an MMP inhibitor].

6. (amended) The method of claim 1 wherein [said] the MMP inhibitor is a tetracycline.

7. (amended) The method of claim 6 wherein [said] the tetracycline is minocycline.

Please cancel claims 8 and 9.

10. The method of claim [1] 5 wherein the TNF-alpha inhibitor is thalidomide.

11. (amended) The method of claim 1 [wherein the first agent is] comprising administering a mast cell inhibitor selected from the group consisting of an antihistamine, a serine protease inhibitor, and a degranulation inhibitor.

12. (amended) The method of claim 1 wherein the [first and second agents] NSAID, inflammatory cytokine inhibitor, or mast cell inhibitor and MMP inhibitor are provided mixed together in a composition.

13. The method of claim 12, wherein the composition is a liquid adapted for use as an oral rinse.

14. The method of claim 12, wherein the composition is a solid adapted for oral ingestion.

Please cancel claims 15-22.

23. (amended) The method of claim 22, wherein [said] the mucositis is induced by chemotherapy.

24. (amended) The method of claim 22, wherein [said] the mucositis is induced by radiation therapy.

25. (amended) The method of claim 22, wherein [said] the patient is a cancer patient preparing to undergo chemotherapy or radiation therapy.

26. (amended) The method of claim 22, wherein [said] the patient is a cancer patient currently undergoing chemotherapy or radiation therapy.

27. (amended) The method of claim 1, wherein [said] the mucositis is oral mucositis.

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AMENDMENT

APPENDIX: Clean Copy of Claims as amended

1. (amended) A method of treating, inhibiting, or preventing mucositis in a human patient, comprising administering to [said] a patient in need of or undergoing radiation treatment or chemotherapy, an NSAID, an inflammatory cytokine inhibitor, or a mast cell inhibitor in combination with an effective amount of an MMP inhibitor to alleviate the symptoms of the mucositis.

2. (amended) The method of claim 1, comprising administering as the NSAID a COX-1 or COX-2 inhibitor.

3. (amended) The method of claim 2, wherein the COX-1 inhibitor is indomethacin or flurbiprofin.

4. (amended) The method of claim 1, comprising administering an inflammatory cytokine inhibitor selected from the group consisting of an IL-6 inhibitor, a TNF-alpha inhibitor, an IL-1 inhibitor, and an interferon-gamma inhibitor.

5. (amended) The method of claim 4 wherein the inflammatory cytokine inhibitor is a TNF-alpha inhibitor.

6. (amended) The method of claim 1 wherein the MMP inhibitor is a tetracycline.

7. (amended) The method of claim 6 wherein the tetracycline is minocycline.

10. The method of claim 5 wherein the TNF-alpha inhibitor is thalidomide.

11. (amended) The method of claim 1 comprising administering a mast cell inhibitor selected from the group consisting of an antihistamine, a serine protease inhibitor, and a degranulation inhibitor.

12. (amended) The method of claim 1 wherein the NSAID, inflammatory cytokine inhibitor, or mast cell inhibitor and MMP inhibitor are provided mixed together in a composition.

13. The method of claim 12, wherein the composition is a liquid adapted for use as an oral rinse.

14. The method of claim 12, wherein the composition is a solid adapted for oral ingestion.

23. (amended) The method of claim 22, wherein the mucositis is induced by chemotherapy.

24. (amended) The method of claim 22, wherein the mucositis is induced by radiation therapy.

25. (amended) The method of claim 22, wherein the patient is a cancer patient preparing to undergo chemotherapy or radiation therapy.

26. (amended) The method of claim 22, wherein the patient is a cancer patient currently undergoing chemotherapy or radiation therapy.

27. (amended) The method of claim 1, wherein the mucositis is oral mucositis.